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EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,288	SCHENK ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,69,70 and 73-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,69,70 and 73-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-28-03, 9-9-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *PTO-1449 4-12-04*.

Detailed Action

1. The amendments filed 12-9-03, 2-9-04 and 10-4-04 have been entered into the record and have been fully considered.

2. Claims 50, 69-70 and 73-100 are pending.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. As a result of applicant's amendment, all rejections not reiterated herein have been withdrawn.

5. Applicant's traversal of the species election requirement in the paper of 10-4-04 on the basis that the species are not mutually exclusive is found persuasive in that claims 90-97 specify that the amyloid deposits are comprised in a tissue sample. Accordingly the species election requirement is withdrawn and claims 50, 69-70 and 73-100 are under examination.

6. The Examiner further notes Applicant's previous traversal in which it is argued that a tissue is a species of biological entity physically associated with an antigen and that a tissue as an aggregation of similarly specialized cells united in performing a particular function.

Priority

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application);

the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). In particular, disclosure of the ex vivo screening assay as at pp. 96-100 of the specification is not noted within the 09/322,289 application. Accordingly, the effective filing date awarded instant claims is that of 5-26-00.

Claim Objections

8. Claim 50, 81, 87 and 90 are objected to because of the following informalities: Clear antecedent basis should be provided within claims, for example in claim 50, line 6, via amendment to "a reduction in *the* amount of *the* tissue sample", in claim 81 to "a reduction in *the* amount of *the* isolated biological entity". Similar amendment should be instituted for the elements of claims 87 and 90. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 74 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 recites the limitation "the brain" in reference to claim 73. There is insufficient antecedent basis for this limitation in the claim.

11. Claims 75 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 75 and 94 recite the limitation "the antigen" in reference to claim 50 and 90, respectively. There is insufficient antecedent basis for this limitation in the claim. "an antigen" is first introduced at claim 69 and is not apparently present previous to claim 94.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 50, 69-70, 77-79, 81-84 and 87-89 are rejected under 35 U.S.C. 102(b)

as being anticipated by Bellotti et al., Renal Failure 15(3):365-371, 1993 as further evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, Inc., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401.

Bellotti et al., teach monoclonal anti-idiotype antibody IgG1k Mab 3B11D4 raised against the λ chain dimmers in AL (amyloid light-chain) amyloidosis. Bellotti conducted panning and cytotoxicity experiments that demonstrate the antibody selectively eliminates the idiotype-positive cells from peripheral blood. The idiotype-positive cells from peripheral blood constitute an aggregation of similarly specialized cells united in performing the particular function of production of light chain immunoglobulin that tis the major constituent of AL amyloid fibrils, see in particular p. 365-366. The panning and complement mediated cytolysis assays are noted at the paragraph spanning pp. 366-367. In particular peripheral idiotype-positive B lymphocytes (tissue) were combined with Mab (antibody) absorbed on microtiter plates in the presence of PBMC (peripheral blood mononuclear cells) phagocytic cells bearing Fc receptors in vitro. In addition a classic complement mediated cytotoxicity assay was performed on enriched B-cell populations from the DEP patient (tissue) and cytotoxicity was scored microscopically as in Figure 5.. Results and noted lysis of B cells (tissue) via antibody is noted at pp. 367-369. While the reference does not extensively discuss the classic cytotoxicity assay, Benjamini further evidences the widely art accepted and recognized principles as disclosed at pp. 136-138 where binding of antibody to antigen enables complement mediated cytolysis. Benjamini further evidences synthesis of the complement components via peripheral blood monocytes (PBMC) (inflammatory cells) as included in

the cytotoxicity assay. Hence Bellotti meets the limitations of claims 50, 69-70, and 77-79. The B cells constitutes an isolated biological entity as it is comprised of proteoglycan, adhesion molecules and tumor antigens (light chain amyloid) and hence the assay meets the limitations of claims 81-84. Moreover, the B cell constitutes a biological entity physically associated with an antigen as the tissue is cancerous (AL amyloidosis), comprises inflammatory cells, a nonmalignant abnormal cell growth and/or abnormal extracellular matrix.. Hence the reference meets the limitations of claims 87-89.

14. Claims 81-83 and 85-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Jahrling et al., J. of Med. Virol., 12:1-16, 1983 as further evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, In c., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401.

Jahrling et al., teach opsonization clearance of alphaviruses in hamsters as well as adsorption of virus/antibody aggregates to macrophages in culture and internalization within vacuoles evidencing clearance of virus/antibody aggregates dependent upon complement-mediated interaction of virus antibody aggregates with cells that possess Fc and complement receptors. In particular both VEE and WEE viruses in the presence of antibody plus complement efficiently adsorbed to hamster macrophages comprising Fc receptors and were internalized indicating clearance, see in particular pp. 9-12, Figure 3, via microscopy and Table V. The in vitro culture assay involves the combination of antibody with isolated biological entity of virus (WEE and VEE) and hamster macrophages (phagocytic cells), monitoring of vius in either medium

or adsorbed to cells. The increased absorption to macrophages indicating internalization and clearance. Hence the reference meets the limitations of claims 81-83, and 85-86.

15. Claims 50, 69-70, 78, 81-83, 85 and 87-88 are rejected under 35 U.S.C. 102(b) as being anticipated by Jorbeck et al., Infection & Immunity, 32(2):497-502, May 1981.

Jorbeck et al., teach the analysis of the specificity and activity of antibodies generated against different *Salmonella* antigens. The analysis is via both in vitro and in vivo phagocytosis assays measuring the ability of either activated peritoneal exudates cells (PEC) or in vivo phagocytic cells comprising Fc receptors to phagocytose and control the growth/replication of Salmonella, see in particular abstract, p. 497, paragraph spanning columns 1-2, pp. 500-501 and Table 4. The in vitro phagocytosis assays are described at p. 498 columns 1-2. The in vitro assays involve combination of PEC exudates containing polymorphonuclear leukocytes, lymphocytes and monocytes-macrophages (phagocytic cells bearing Fc receptors), with pre- or post-vaccination serum (comprising antibodies). The *Salmonella* is a suitable tissue sample as in claim 50 as the Salmonella represents a group or aggregation (as administered) of similarly specialized infectious cells. The Salmonella is also a suitable isolated biological entity as in claim 81 and a biological entity physically associated with an antigen as in claim 87. The assay notes monitoring the clearance of the Salmonella bacteria via phagocytosis. The results of the various antibodies in effecting clearance in vitro and in vivo are shown at pp. 498-502, Figures 2-3 and Tables 1-4. The in vitro analysis is further deemed to be in tissue in that the Salmonella cells are an aggregate of similarly

specialized cells that are united in the performance of a particular function (here infection). Here the PEC exudates are phagocytic cells bearing Fc receptors and are involved in the lysis of Salmonella in vitro as in Table 4. Thus the reference teachings meet the limitations of claims 50, 69-70, 78, 81-83, 85, and 87-88.

16. Claims 50, 69-70, 77, 79, 81-82, 84, 87 and 89 are rejected under 35 U.S.C. 102(b) as being anticipated by Herlyn et al., J. Immunol., 1979, 9:657-659 as further evidenced by evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, Inc., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401.

Herlyn teach monoclonal antibodies tested for cell-mediated cytotoxicity against human melanoma and colorectal carcinoma tissue samples isolated from patients and maintained in culture. In particular the assay notes combination of target cancer cell lines WM-8 and WM-9 with monoclonal antibodies and followed by incubation with spleen effector cells as noted, pp. 657-658. The clearance of cancer cells was indicated as a function of cell lysis and chromium release and hence the monitoring is inclusive of where the cell/tissue or antigen is either present or absent as indicated via chromium release. Benjamini further notes the principles of the ADCC assay as noted for example at pp. 73-74, 372-373 and 400-401 including cytolysis mediated via antigen/antibody binding. Hence the reference teachings anticipate claims 50, 69-70, 77, 79, 81-82, 84, 87 and 89.

17. Claims 50, 69-70, 73, 77-79, 81-84, 87-92, 96-97 and 99 are rejected under 35 U.S.C. 102(e) as being anticipated by Solomon et al., WO 99/60024, 25 November 1999.

Solomon et al., teach methods for amyloid removal using anti-amyloid antibodies that enhance the cell-mediated immune response to deposits of amyloid and exploit the opsonizing effect of antibodies directed toward amyloid material, fibrils or its component parts both in vivo and in vitro. In particular, Figure 2A and 2B note in vitro adherence of human neutrophils (phagocytic cells bearing Fc receptors) after the amylid plaques were treated with anti-human IgLC monoclonal antibodies showing that the mouse mAb can bind to human amyloid as well as attract human neutrophils, see in particular pp. 18 and Figure 2. Thus, the reference teachings anticipate claims 50, 69-70, 73, 77-79, 81-84, 87-92, 96-97 and 99.

18. Claims 50, 69-70, 73, 74-84, and 87-100 are rejected under 35 U.S.C. 102(e) as being anticipated by Vitek et al., US Patent No. 5,935,927 Aug. 10, 1999, filed Aug. 10, 1996 as further evidenced by evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, Inc., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401.

Vitek et al., teach compositions and methods for stimulating amyloid removal in amyloidogenic diseases using advanced glycosylation endproducts. In particular the method includes stimulating mechanisms of recognition and removal of AGE-amyloid in an animal to remove the amyloid plaques via scavenger systems such as phagocytic cells, macrophages and in neural tissue microglial cells, see in particular column 6, line 36-column 7, line 33. A particular embodiment of the invention includes wherein the therapeutic agents include antibodies to AGE-amyloid, in particular antibodies to AGE-beta amyloid, see in particular column 7, lines 11-16, column 12, lines 46-67, column

15, column 16, lines 44-52. In addition, Vitek teaches where the effectiveness of an AGE bearing targeting agent can be tested for efficacy, see in particular column 21-22, paragraph spanning and column 24, lines 13-25, including the use of in vitro and in vivo assays, see in particular column 22, line 54-column 23, line 14. In particular, the method provides for combination of anti-AGE antibody, various antigens including beta amyloid antigen in vivo and in culture with phagocytic cells, including microglia with monitoring of the amount of AGE modified protein/antigen/biological entity (including AGE-beta amyloid) amongst samples and over time. The antibodies of Vitek include polyclonal and monoclonal antibodies, see in particular column 15, lines 26-58. Polyclonal antibodies are evidenced to bind to epitope within amino acid residues 1-7 of beta amyloid, see in particular pp. 96-100 of instant specification. The assays may be in vitro and in biological tissue, particularly where the tissue is from the brain of an animal having amyloid plaques or Alzheimer's pathology. Animal tissue comprises inflammatory cells and Alzheimer's plaques are considered nonmalignant abnormal cell growth. Moreover, the in vitro analysis may be in tissue sections viewed and fixed via microscopy on microscope slides as disclosed at column 32 Example 2. Such ADCC assays are widely accepted in the art as evidenced via Benjamini et al. In particular, Benjamini further evidences synthesis of the complement components via peripheral blood monocytes (PBMC) (inflammatory cells) as included in the cytotoxicity assay and Benjamini further notes the principles of the ADCC assay as noted for example at pp. 73-74, 372-373 and 400-401 including cytolysis mediated via antigen/antibody binding. Thus, the reference teachings anticipate claims 50, 69-70, 73, 74-84, and 87-100.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 50, 69-70 and 73-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitek et al., US Patent No. 5,935,927 as further evidenced by evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, Inc., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401, Solomon et al., WO 99/60024, 25 November 1999, Herlyn et al., J. Immunol., 1979, 9:657-659, Jahrling et al., J. of Med. Virol., 12:1-16, 1983, Bellotti et al., Renal Failure 15(3):365-371, 1993 and Jorbeck et al., Infection & Immunity, 32(2):497-502, May 1981.

Vitek notes treatment in vivo of Alzheimers via administration of AGE amyloid antibodies and further notes in vitro assays for assessing plaque mediated clearance. In particular Vitek notes that "Further testing for clearance of the AGE-modified insoluble βAP (beta amyloid peptide) can be conducted by incubation with cultured phagocytic cells such as mouse peritoneal macrophages, elicited macrophages, the RAW 264.7 cell line, human peripheral monocytes or microglia or astroglia primary cells or cell lines." Other in vitro assays for assessing antigen uptake via cytolytic or phagocytic cells are noted for example at columns 22-23. Vitek further notes assessment of such phagocytic activity in vivo, see in particular column 16-24.

However, Vitek does not specifically exemplify the noted phagocytic assay in

vitro where the tissue is of Alzheimer's disease patient with antibody binding to epitope within residues 1-7.

Yet one of skill in the art is highly versed in assessing the ability of any antibody to mediate clearance of an antigen or cell via phagocytosis or cytolysis as evidenced via Benjamini, Solomon, Herlyn, Jahrling, Bellotti and Jorbeck both in vitro and in vivo as noted above. One of skill in the art would be motivated to assess such activity in vitro given the successful teachings of the AGE-beta amyloid antibody in vivo to mediate clearance of amyloid plaques as taught via Vitek. The reference provides guidance to the particular selection of antibodies reactive with beta amyloid, that are monoclonal or polyclonal, to the the proper tissues substrate comprised of amyloid plaques and to the relevant phagocytic cells that have already shown to be effective in mediating opsonization and/or cell mediated cytotoxicity as directed via antibodies administered in vivo. The reference specifically suggests the performance of this same assay in vitro as noted for example at column 22-23. The performance of the assay in vitro provides for the superior advantages of an easily reproducible cell culture system that obviates the need for in vivo experimentation which is often unpredictable in nature, not easily reproduced, expensive and involves numerous ethical considerations particularly with the experimentation required in human cells and tissues. One of skill in the art would have an expectation of success utilizing such in vitro assays as ADCC and opsonization are art accepted principles and the performance of such assays either in vitro or in vivo are widely and routinely practiced in the art. Thus, the cumulative reference teachings render the claimed invention obvious to one of skill in the art.

Status of Claims

20. No claims are allowed.

21. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
December 10, 2004

SHARON L. TURNER, PH.D.
PATENT EXAMINER